Answer 1:

**Bibliographic Information**

**Cisplatin represses transcriptional activity from the minimal promoter of the O6-methylguanine methyltransferase gene and increases sensitivity of human gallbladder cancer cells to 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-2-chloroethyl)-3-nitrosourea.** Sato, Ken; Kitajima, Yoshihiko; Nakagawachi, Tetsuji; Soejima, Hidenobu; Miyoshi, Atsushi; Koga, Yasuo; Miyazaki, Kohji. Department of Surgery, Department of Biomolecular Sciences, Saga University Faculty of Medicine, Saga, Japan. Oncology Reports (2005), 13(5), 899-906. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 143:638 AN 2005:407240 CAPLUS 

**Abstract**

O6-Me guanine methyltransferase (MGMT) repairs O6-alkylguanine in cellular DNA introduced by the clin. used alkylating drug 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU). Thus, cancer cells with MGMT expression are resistant to ACNU treatment. Cisplatin has been reported to suppress MGMT expression; however, the mol. mechanism by which cisplatin reduces MGMT expression remains to be elucidated. Using gallbladder cancer cells (KMG-C) expressing MGMT, we analyzed whether a low dose of cisplatin suppresses MGMT expression, followed by an enhanced drug effect of ACNU in vitro and in vivo. We also investigated the promoter region crit. for the transcriptional repression of MGMT gene by cisplatin using 5 deletion mutants in reporter promoter assays. In RT-PCR anal., the expression of MGMT mRNA in KMG-C cells was dose- and time-dependently repressed. Drug sensitivity to ACNU was increased 2-fold by pretreatment with cisplatin, compared with only ACNU treatment, in MTT assays as well as tumor-bearing nude mice. Although the 5'-flanking region is deleted as far as -69 bp upstream of the transcription start site, cisplatin dose dependently inhibited luciferase activity. However, cisplatin did not cause such repression when 59 bp region from -69 to -10 bp was deleted. We confirmed that cisplatin enhanced sensitivity to ACNU in KMG-C cells expressing MGMT both in vitro and in vivo. Furthermore, a low dose of cisplatin repressed the transcription of the MGMT promoter. The 59 bp region in the MGMT promoter was crucial for repression by cisplatin. These results might form the basis of a chemotherapeutic strategy involving alkylating agents via prior cisplatin-induced biochem. modulation.

Answer 2:

**Bibliographic Information**

**In vivo inhibitory effect of anticancer agents on human pancreatic cancer xenografts transplanted in nude mice.** Imai, Shiro; Nio, Yoshinori; Shiraishi, Takahiro; Manabe, Tadao; Tobe, Takayoshi. Fac. Med., Kyoto Univ., Kyoto, Japan. Anticancer Research (1991), 11(2), 657-64. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 115:174179 AN 1991:574179 CAPLUS 

**Abstract**

Pancreatic cancer is one of the neoplasms resistant to chemotherapy. In the present study human pancreatic cancer xenografts (3 adenocarcinomas and 1 cystoadenocarcinoma) were s.c. transplanted in nude mice and after the tumors grew to 100-300 mm3, the mice were i.p. administered with mitomycin C (MMC), adriamycin (ADR), 5-fluorouracil (5-FU), carboquone (CQ), cisplatinum (CDDP), nimustine chloride (ACNU) or DWA2114R at 1/3 LD50 on days 0, 4, and 8. The tumor sizes on day 12 were compared with those on day 0. MMC and CQ significantly inhibited the tumor growth of 3 lines, and ACNU, CDDP and ADR inhibited the growth of 1 line. Further, 5-FU, futrafur, carmofur, UFT, and L-phenylalanine mustard (L-PAM) were orally administered to mice into which 1 adenocarcinoma line had been transplanted. While none of fluoropyrimidines inhibited tumor growth, L-PAM at 4 mg/kg significantly inhibited growth, although it was accompanied by severe body wt. loss. In the present study several agents significantly inhibited tumor growth, but none of them could induce the regression of the tumor when used singly. These results suggest that CQ, ACNU, CDDP and L-PAM may be applied to the chemotherapy of pancreatic cancer. However, the effect of a single agent is restricted and the development of new combination treatments is urgently required.

Answer 3:

**Bibliographic Information**

**Preliminary experimental results with the nitrosourea derivative ACNU in the treatment of malignant gliomas.** Bamberg, Michael; Budach, Volker; Stuschke, Martin; Gerhard, Lieselotte. Dep. Radiat. Oncol., West Ger. Tumour Cent., Fed. Rep. Ger. Radiotherapy and Oncology (1988), 12(1), 25-9. CODEN: RAONDT ISSN: 0167-8140. Journal written in English. CAN 109:47958 AN 1988:447958 CAPLUS 

**Abstract**

The cytotoxic effectiveness of the nitrosureas ACNU (Nimustine) and BCNU (Carmustine) were compared at equitoxic doses in xenografts from 2 astrocytomas grades III/IV (Li, Re) and 1 oligodendroglioma grade III (Oe) in nude mice. Growth delays of 18.7 days (ACNU) and 2.4 days (BCNU) for the Li-xenograft were obsd. at an LD10 for both drugs. For the Re- and Oe-xenografts, growth delays of 18.0 vs. 14.0 days and >27.0 vs. 14.2 days were obsd. at an 33 mg/kg of ACNU or BCNU, i.p., resp. Apparently, there is a therapeutic advantage with ACNU for these high grade gliomas.